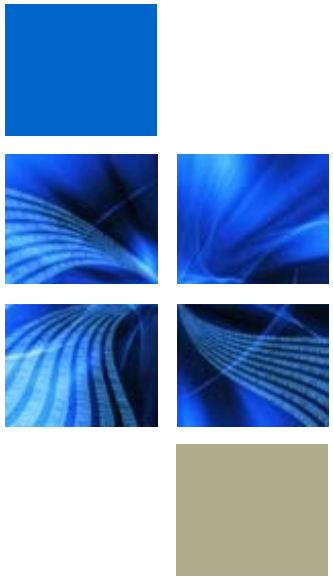
The Value of Patient Registries in Clinical Research



June 4, 2008

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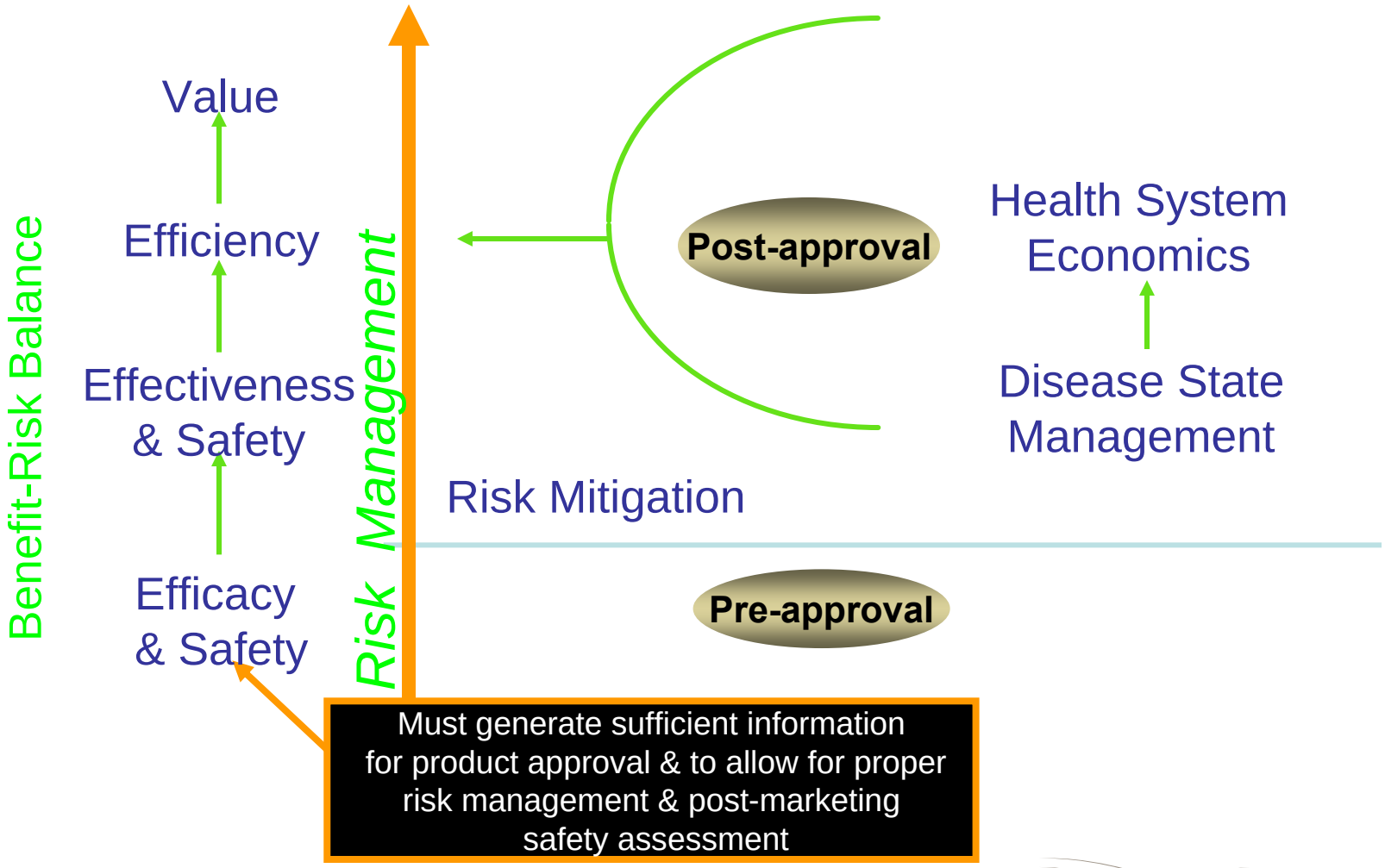
Agenda

- Regulatory Guidance & Registry Definitions
- Benefits, Limitations & Challenges of Patient Registries
- Applications of Patient Registries
  - Effectiveness Data
  - Safety Data
  - Hypothesis Generation & Supportive Clinical Data
  - Humanistic & Economic Outcomes
  - Treatment Patterns & Product Utilization
  - Standards of Care & Quality Improvement

Evolving Perspective on Healthcare



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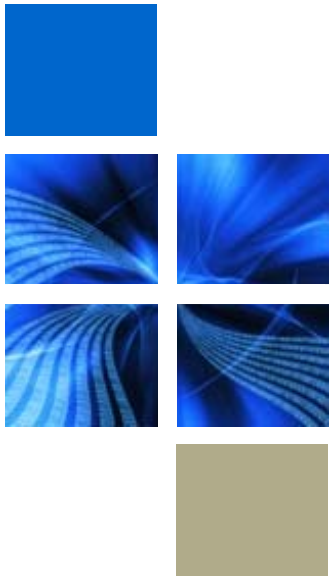
Benefits, Limitations & Operational Challenges of Patient Registries



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Final Guidance Documents – March 2005*

- Pre-marketing Risk Assessment
- Development & Use of Risk Minimization Action Plans
- Good Pharmacovigilance Practices & Pharmacoepidemiologic Assessment

**http://www.fda.gov/cder/guidance/6358fnl.htm*

Definition of a Registry

- **Guidance for Industry: *Good Pharmocovigilance Practice and Pharmacoepidemiologic Assessment***

http://www.fda.gov/cder/guidance/index.htm

"an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health events."

United States Department of Health & Human Services

AHRQ Agency for Healthcare Research and Quality

Advancing Excellence in Health Care www.ahrq.gov

Registries for Evaluating Patient Outcomes: A User's Guide

Final Research Report published 16 May 2007

http://effectivehealthcare.ahrq.gov/reports/new_research.cfm

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Definition of a Registry

AHRQ

Registries for Evaluating Patient Outcomes: A User's Guide

"A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes."

Benefits of Registries

- Obtain ‘real world’ therapeutic effectiveness and safety data
- Large patient numbers can detect rare adverse events
- Heterogeneity among numerous investigative sites
- Research collaboration with interactive communication & data reporting to investigators
- Usual diagnostic and follow-up procedures can be used rather than “research” procedures
- Can be conducted in any phase of product development

Benefits of Registries

- Flexible, multi-faceted, e.g., sub-studies
- Study subjects are heterogeneous
  - Various treatments
  - Concomitant meds
  - Co-morbidities
- Hypothesis generation when an a priori hypothesis is difficult to define
- Supportive data for label extensions
- Evidence-based medicine for outcomes & reimbursement
- Cost effective on a per patient basis

Limitations of Registry Data

- Non-randomized data cannot be used for promotional or competitive claims
- Data generally not 100% verified
- Variability in data definitions, interpretation, abstraction & collection intervals
- Selection bias due to non-sequential patients

Limitations of Registry Data

- Inability to perform desired analyses due to limitations of data captured
- Capture of irrelevant data that is not, or cannot be reported
- Analysis of observational data requires experienced biometrics personnel
- Perceived diminished value of research evidence than controlled trials
- Journal reviewers may be less accepting of observational data

Operational Challenges of Registries

- Research naïve investigators & sites
- Site may not have a trained Study Coordinator
- Enrolling & training large numbers of sites
- Capture & cleaning of large volumes of data
- Site & patient retention
- Determining the appropriate balance of on-site/escalated monitoring vs. remote site management
- Under-reported & hidden SAEs

How is a Registry "different" from a RCT?

Registry

- Effectiveness
- Observational
- "Real world"
- Hypothesis generating
- Large "N"
- Flexible
- GCP optimal
- Opportunistic or mandatory

RCT

- Efficacy
- Randomized
- Controlled / selection criteria
- Hypothesis driven
- Small "N"
- Powered
- GCP required
- Usually mandatory

Applications of Patient Registries

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Applications of Patient Registries

- Effectiveness data
- Safety data
- Hypothesis generation & supportive data
- Humanistic & economic outcomes
  - Patient reported outcomes
  - Compliance/tolerability/satisfaction
  - Cost effectiveness
  - Reimbursement
- Treatment patterns & product utilization
- Continuous quality improvement & standards of care

Effectiveness & Safety Data

NDA Studies include a limited number of patients and a limited treatment duration. Post launch, a large and diverse patient group is exposed.

Effectiveness & safety data are necessary to evaluate:

- Exposure to the population at large
- Effect of co-morbidities not previously evaluated
- Use of concurrent medications and drug-drug interactions
- Generalization to clinical practice
- Clinician understanding of the label and product use

Effectiveness & Safety Data

Effectiveness & safety data can be used to:

- Detect rare, unknown or evolving adverse events in real-world clinical practice
- Describe the natural history of a disease state
- Provide baseline and temporal trends in treated vs. untreated patients
- Observe relationships among a disease state, practice patterns and patient outcomes
- Characterize a product's *long-term* effectiveness and safety
- Characterize "off-label" product use

Safety Data

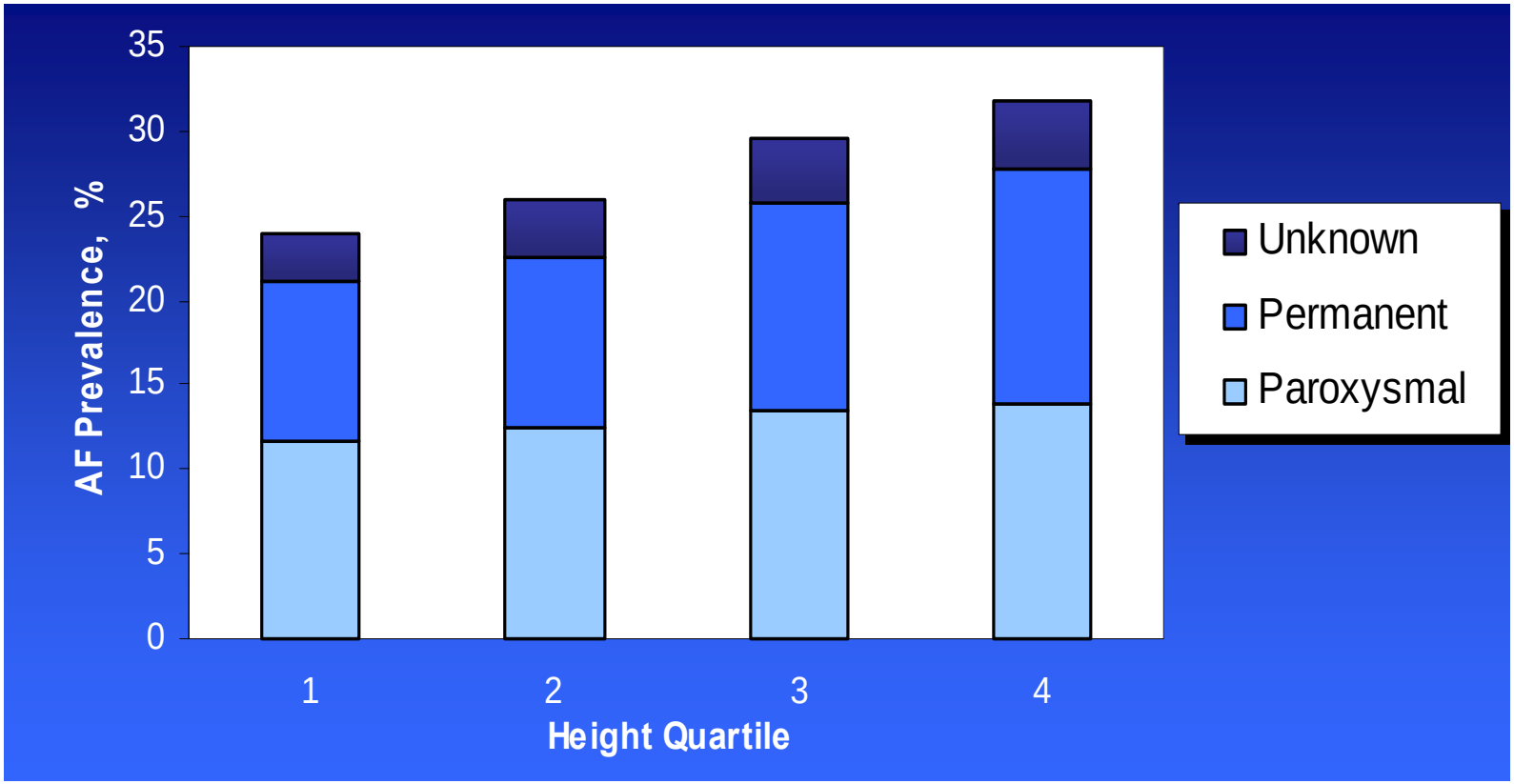
Benign intracranial hypertension associated with growth hormone therapy

Malozowski S, Tanner LA, Wysowski D, Fleming GA, &StadelBV. Benign intracranial hypertension in children with growth hormone deficiency treated with growth hormone. *J Pediatr* 1995; 126: 996-9.

"We thank the staffs of Genentech, Lilly, Novo-Nordisk, Pharmacia, and Serono, and the members of the National Cooperative Growth Study, for their assistance in collecting and sharing the data for this manuscript."

Safety Data

Prevalence of atrial fibrillation (AF) patterns according to height quartiles*



***The Relationship Between Stature and the Prevalence of Atrial Fibrillation in Patients with Left Ventricular Dysfunction;** Hanna, B. Heeke, H. Bush, L. Brosius, D. King-Hageman, J. Beshai, and J. Langberg; Journal of the American College of Cardiology; Nov. 2005.

Hypothesis Generation & Supportive Data

Daily subcutaneous injections of growth hormone

Kemp SF and the *National Cooperative Growth Study*. Dose frequency of growth hormone administration: two-year data comparing daily and three times per week. *Pediatr Res* 1993; 33 (Suppl):S46.

Hypothesis Generation & Supportive Data

Growth hormone treatment of short stature in Turner syndrome

Plotnick L, Attie KM, Blethen S, Sy J. Growth hormone treatment of girls with Turner syndrome: the *National Cooperative Growth Study* experience. *Pediatrics* 1998; 479 481.

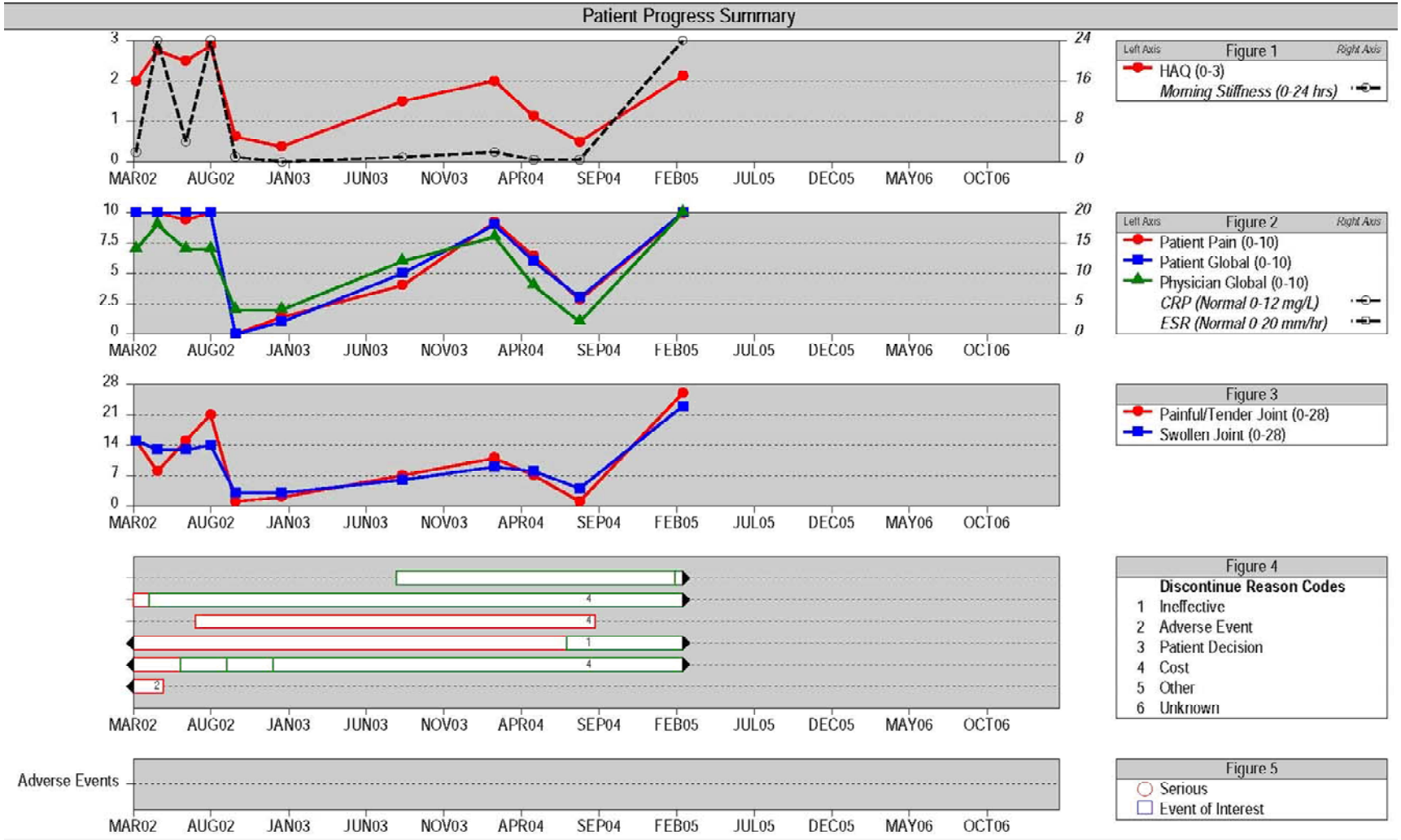
Humanistic & Economic Outcomes

- Patient reported outcomes (PROs)
  - Product utilization
  - Quality of Life (QOL)
  - Patient satisfaction
- "Real-world" humanistic measures
  - Supplement existing or ongoing (PE) analysis
  - Validate Centers for Medicare & Medicaid Services (CMS) data
  - Identify key cost drivers
  - Support reimbursement & expanded patient access
- Cost data
  - Obtained directly
  - Apply standard costs based on:
    - Frequency & type of procedures
    - Hospitalization, etc.

Patient Reported Outcomes

- PROs obtained from patients at physician visit or via remote patient contact
- PRO instruments completed via: paper, IVRS, Computer-Assisted Telephone Interview (CATI), ePRO (web based), PDA, other
- Effectiveness data
- Patient & physician satisfaction with treatment
- Data on treatment compliance & tolerability

Sample Patient Profile in RA



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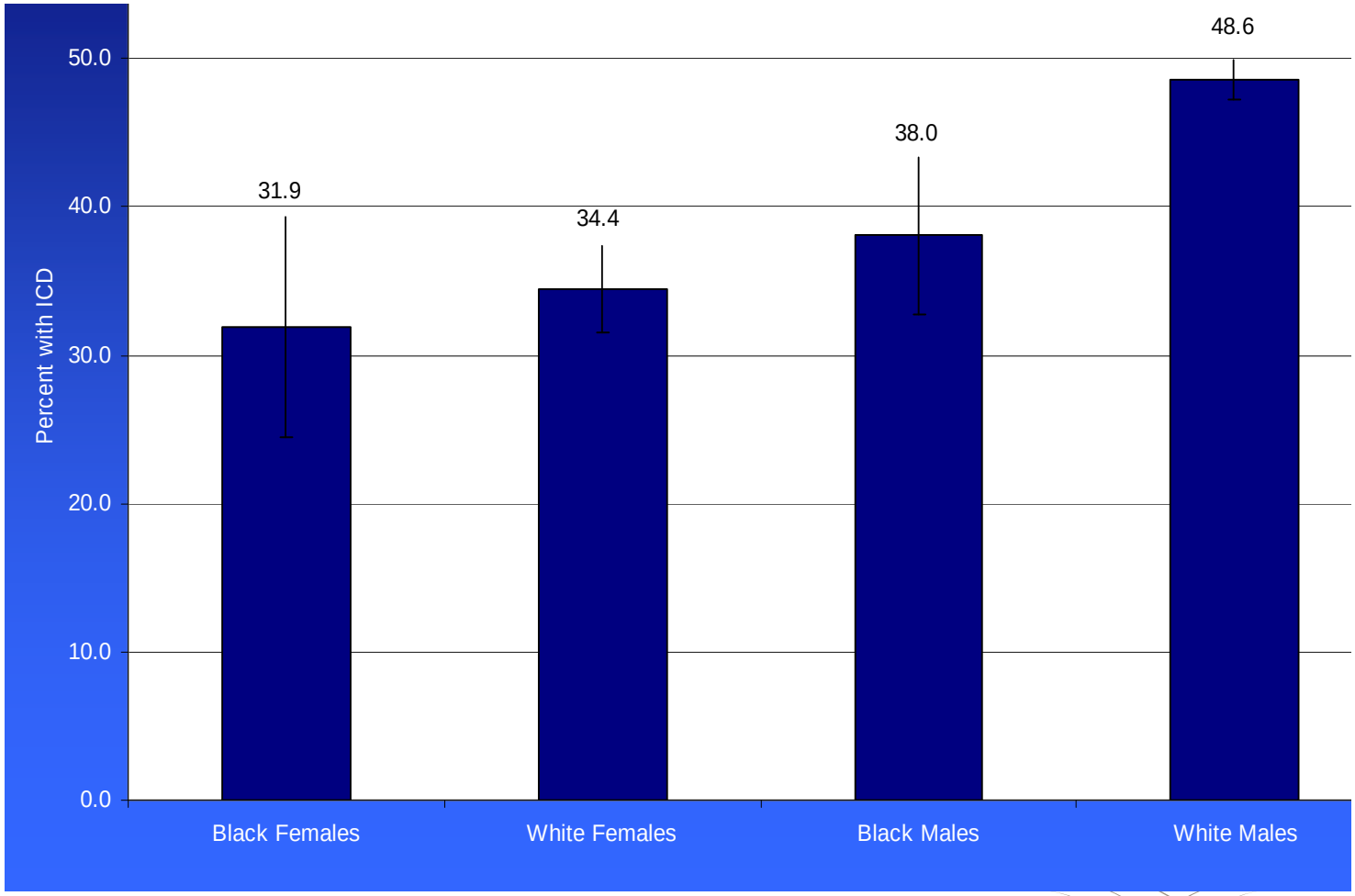
Treatment Patterns & Product Utilization

- Physician practice patterns
- Temporal patterns of treatment
- Product adoption
- Factors impacting prescribing decisions
- Under-treated patient populations
- Issues related to product use, e.g., tolerability, compliance
- Characterize off-label use (unsolicited)
- Competitive product information

Treatment Patterns & Product Utilization

ICD Prevalence: Comparison of Gender & Race*



Racial Differences in Implantable Cardioverter-Defibrillator Utilization Among Patients with Prior Myocardial Infarction and Ejection Fraction ≤ 35%; K. Thomas, S. Al-Khatib, R. Kelsey, L. Brosius, B. Raleigh, F. Gilliam; Oral presentation for American Heart Association (AHA), Nov 2005

Treatment Patterns & Product Utilization

Sex-based Differences in Early Mortality After Myocardial Infarction

Vaccarino V, Parson L, Every N, et al. *NEJM* 1999:341 (4):217-25 (NRMI 2)

- 1658 hospitals
- 348,878 patients (155,565 women; 229,313 men)
- Overall mortality rate during hosp: 16.7% women; 11.5% men
- Patients <50 yo mortality rate for women was twice that of men
- No longer significant after age 74 ($p<0.001$)

"After MI, younger women, but not older women, have higher rates of death during hospitalization than men of the same age."

"Younger women with MI represent a high-risk group deserving of special study."

Standards of Care & Quality Improvement

- Define “best practice guidelines & critical pathways
- Standards of care defined by professional societies
- Promote continuous quality improvement (CQI)
- Performance measurement tool for accreditation
- Centers for Medicare and Medicaid Services (CMS) reimbursement
- Data benchmarking-site vs. aggregate data

Standards of Care & Quality Improvement

A Comparison of the National Registry of Myocardial Infarction 2 with the Cooperative Cardiovascular Project (CCP).

Every N, Frederick P, Robinson M, et al. *J Am Coll Cardiol.* 1999; 33: 1886-94 (NRMI 2).

- NRMI 2: 1,529 hospitals; 446,970 patients
- CCP: 4,223 hospitals; 224,377 patients
- Identified 35,675 NRMI 2 & 42,703 CCP patients who were Medicare eligible (> 65 yo) & who were admitted to the same hospitals during the same data abstraction period
- Matched 25,664 patients

"We conclude that the simpler case ascertainment and data collection strategies employed by NRMI 2 result in process and outcome measures that are comparable to the more rigorous methods utilized by CCP. Outcomes that are more difficult to measure from retrospective chart review such as stroke and recurrent MI must be interpreted cautiously."

Standards of Care & Quality Improvement

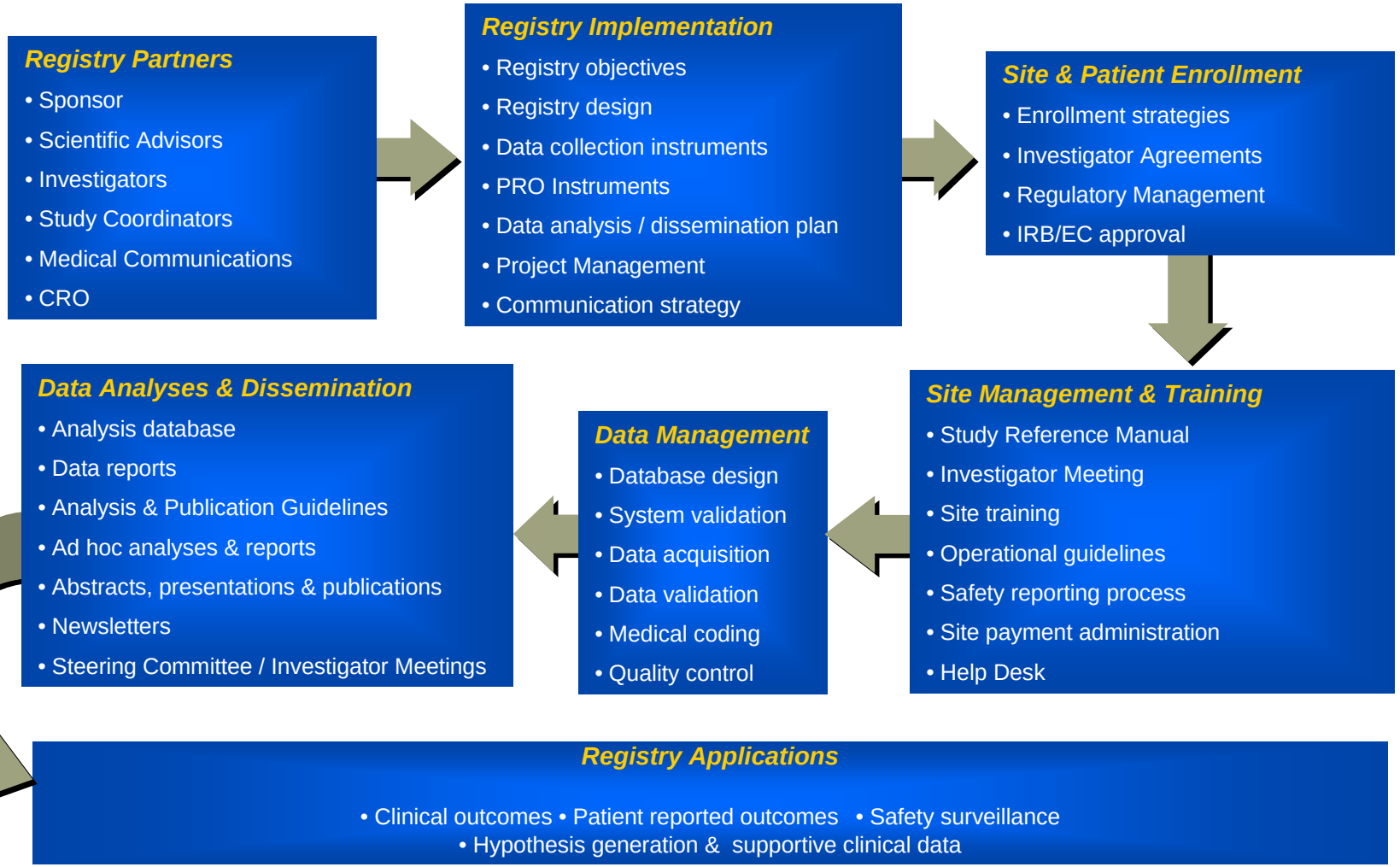
Factors Influencing Time to Thrombolysis in Acute Myocardial Infarction.

Lambrew CT, Bowlby, LJ, Rogers WJ, et al. *Archives of Int Med.* 1997; 157;22:2577-2582 (NRMI 2).

- NRMI 2: Substudy – Time to Thrombolysis
- 42 hospitals
- 1,755 patients
- Collected data on the NHAAP 4 "D's" (Door, Data, Decision, Drug)

"...contacting the primary care physician prior to the initiation of a lytic drug, cardiology consultation, and the preparation of the drug in the pharmacy rather than the ED, significantly delayed the goal of early treatment of patients with ST segment elevation AMI. Delays in the hospital arrival for women are compounded by delays in the decision to treat them."

Registry Planning & Execution



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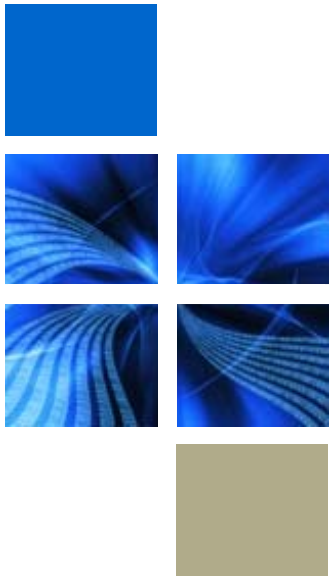
Questions?



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